Nonalcoholic steatohepatitis related acute on chronic liver failure is rising among liver transplant registrants in the United States

Short Title: NASH and transplant listing for ACLF

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List of Abbreviations:
Acute on chronic liver failure (ACLF)
Alcoholic liver disease (ALD)
Hepatitis C virus (HCV)
Non-alcoholic steatohepatitis (NASH)
Model for end-stage liver disease-sodium (MELD-Na)
United Network for Organ Sharing (UNOS)
United States (US)

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Abstract

Background and aims: Acute on chronic liver failure (ACLF) yields the highest risk of short-term mortality, along the spectrum of cirrhosis. We evaluated whether the rising prevalence of nonalcoholic steatohepatitis (NASH) in the United States is reflected among waitlist registrants with ACLF.

Methods: We analyzed the United Network for Organ Sharing (UNOS) registry, years 2005-2017. Patients with ACLF were identified using the EASL-CLIF criteria and categorized into those with NASH, alcoholic liver disease (ALD), and hepatitis C virus (HCV) infection. Statistical analysis included linear regression and Chow's test to determine significance and divergence in trends, and Fine and Grey's competing risks and Cox proportional hazards regression to assess waitlist outcomes.

Results: Between 2005 and 2017, waitlist registrants for NASH-ACLF rose 331.6% ($p<0.001$). ALD-ACLF increased 206.3% ($p<0.001$), while HCV-ACLF declined 45.2% ($p=0.018$). This increase in NASH-ACLF occurred across all UNOS regions, rising by 666.7% in region 11. The NASH-ACLF population is aging, and currently 31.5% of the group is age 65 or older. Although NASH-ACLF candidates did not have greater 90-day waitlist mortality (SHR=0.84, 95% CI 0.77-0.92) relative to other etiologies, since 2014, 90-day waitlist mortality has improved for ALD-ACLF (HR=0.78, 95% CI 0.70-0.88) and HCV-ACLF (HR=0.76, 95% CI 0.67-0.85) but not for NASH (HR=0.93, 95% CI 0.81-1.08).

Conclusions: NASH is the fastest rising etiology of cirrhosis among transplant registrants with ACLF in the United States. Since 2014, waitlist outcomes have

improved for ALD-ACLF and HCV-ACLF, but not for NASH-ACLF. With the aging NASH population, patients with NASH-ACLF may eventually have the highest risk of death on the waiting list.

Introduction

The prevalence of nonalcoholic steatohepatitis (NASH) has risen markedly in the past decade and is expected to increase by 63% in 2030, comprising 33.5% of the population in the United States (US).[1] Whereas hepatitis C virus (HCV) was previously the predominant reason for liver transplantation (LT) listing, studies are now demonstrating alcoholic liver disease (ALD) to be the most common etiology among transplant candidates[2, 3], followed by NASH.[4] Although this shift is partially attributed to direct acting antiviral therapy for HCV, the concurrent elevation in the prevalence of obesity and diabetes in the US indicates that the burden of NASH is genuinely rising.[5, 6] In the non-transplant setting, NASH has also increased significantly as a cause of cirrhosis related mortality, increasing by 15.4% between 2007-2016.[7]

Although the rising prevalence of NASH has been demonstrated among LT candidates, gaps in the literature still remain. For instance, prior studies have evaluated etiology-based trends for transplant listing secondary to either decompensated cirrhosis or hepatocellular carcinoma.[3, 4, 8] However, there are currently no published data regarding whether the increasing burden of NASH is also occurring among transplant candidates with acute on chronic liver failure (ACLF), which is clinically and pathophysiologically distinct from decompensated cirrhosis[9, 10] in several aspects related to transplantation. First, ACLF is associated with a reduced response to full supportive treatment for certain conditions such as antibiotics for infection[11] or terlipressin for hepatorenal syndrome[12], which may escalate waitlist mortality. Secondly, the survival probability associated with ACLF may not be fully reflected in the model for end stage liver disease-sodium (MELD-Na) scoring system[13, 14], particularly among patients with severe ACLF and extra-hepatic organ failures. Finally, the

presence of three or more organ failures at the time of transplantation may yield diminished post-LT survival, particularly in the elderly.[13, 15, 16] As ACLF represents the sickest point along the spectrum of end-stage liver disease, it is important to understand the epidemiology of liver disease leading to transplant listing for this condition. Therefore, we evaluated etiology-based trends in waitlist registration among patients listed with ACLF, focusing primarily on NASH cirrhosis, to determine if findings in prior studies reporting the rising burden of this condition in the US are corroborated in the ACLF population. We explored national and regional trends concerning the prevalence of NASH, HCV, and ALD among patients listed with ACLF, along with changes related to age and gender, and waitlist outcomes.

Patients and Methods

The study protocol was approved as exempt from review by the institutional review board at Cedars-Sinai Medical Center. The study and analysis of this study was performed consistent with STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) guidelines.[17]

United Network for Organ Sharing (UNOS) database analysis

From the UNOS registry, we evaluated patients age 18 or older listed for liver transplantation from 2005 to 2017. We collected data about patient characteristics at the time of waitlist registration, as well as information regarding waitlist outcomes. MELD-Na score at listing was rounded to the nearest whole number and capped at a score of 40. Regarding etiology of liver disease, we focused our study on candidates who had non-alcoholic steatohepatitis (NASH), alcoholic liver disease (ALD) or hepatitis C (HCV), which are the three most common causes of cirrhosis in the United States. Patients were considered as having NASH as their primary etiology of cirrhosis if they were identified either as having NASH cirrhosis or cryptogenic cirrhosis with a concurrent diagnosis of diabetes mellitus or a body mass index (BMI) above 30 kg/m2, as done in previous studies.[4, 18] To avoid misclassification, patients who were categorized as having both HCV infection and ALD were considered as having HCV, due to lack of data regarding alcohol use.

Identification of ALCF

ACLF at the time of waitlist registration was identified based on the European Association for the Study of the Liver-Chronic Liver Failure (EASL-CLIF) criteria of having a single hepatic decompensation of either ascites or hepatic encephalopathy

and the presence of the following organ failures: single renal failure, single non-renal organ failure with renal dysfunction or hepatic encephalopathy, or two non-renal organ failures.[10] (Table S1) Although bacterial infection and variceal hemorrhage are also decompensating events, information regarding these conditions was unavailable in the UNOS database. Specific organ failures were determined according to the CLIF consortium organ failures score for coagulopathy, liver failure, renal dysfunction and renal failure, neurologic failure, and circulatory failure.[10] We used mechanical ventilation as a surrogate marker for respiratory failure. Grade of ACLF was determined based on the number of organ failures at listing and transplantation. (Table S1)

Statistical analysis

All statistical analyses were performed using the Stata statistical package (version 14, Stata Corporations, TX). Comparisons were made utilizing Chi-square testing for categorical variables and analysis of variance or Wilcoxon rank-sum testing to compare continuous variables between groups. Trends regarding the prevalence of ALD, NASH and HCV among patients listed with ACLF were reported by calculating the percentage difference between years 2005 and 2017. We also calculated the annual percentage change (APC) across the study period, using a two point estimator based on a previously derived formula.[19] To highlight relative changes in etiology accounting for a rising volume of ACLF listings over time, we additionally plotted trend lines divided by the total number of ACLF listings per year. Given apparent linearity in trend lines by visual inspection, we used linear regression to estimate statistical significance of trends and associated beta coefficients, using a threshold p-value <0.05. In the case of HCV listings, however, we estimated separate regression models pre-2014 and post-2014

given the introduction of direct acting antiviral therapy. Statistical differences in the divergence of trends were determined using the Chow test, which compares beta coefficients between regression models. We assessed for risk factors related to waitlist mortality using Fine and Gray's competing risks regression, where LT was the competing event, as well as Cox proportional hazards regression. We combined death or removal from the waiting list for being too sick as a single outcome for waitlist mortality. Variables for our models were selected *a priori.* Goodness of fit was tested using Cox-Snell residuals.

Results

Study population

A total of 20,587 patients with ACLF at time of waitlist registration were studied, of which 4,191 (20.4%) had NASH, 7,624 (37.0%) had ALD induced cirrhosis, and 8,772 (42.6%) had cirrhosis form HCV (figure S1). Table 1 describes the characteristics of the study population at listing. Regarding demographic features, patients with NASH were older (median age 60), and had a significantly smaller proportion of males (48.7%) compared with ALD (73.0%) and HCV (72.0%). The NASH-ACLF group had the greatest percentage of Caucasian patients (75.5%) and whereas those with HCV had the highest proportion of African-Americans (17.4%). Median model for end-stage liver disease-sodium (MELD-Na) score was highest among those listed with ALD (32).

In our analysis of organ failures, we observed that patients listed for ALD had the greatest prevalence of liver failure (45.6%), circulatory failure (10.3%), coagulation failure (38.6%), brain failure (20.1%) and requirement for mechanical ventilation (7.5%). However, candidates with NASH had the highest percentage of renal failure (72.0%). Regarding grade of ACLF, patients listed with NASH had the highest percentage of ACLF-1 (59.9%), while those listed with ALD had the greatest prevalence of ACLF-2 (30.5%) and ACLF-3 (20.6%).

National trends among listed patients

Between years 2005 and 2017, the total number of patients listed with ACLF increased significantly from 1,165 to 2,063 (β=88.3, $p<0.001$), indicating a rise of 77.1%, and an APC of 4.9%. (figure 1a, table S2) After excluding patients with HCC, we similarly found a growth in patients listed with ACLF from 1,142 in year 2005 to 1,998 in

2017 (β=83.7, p<0.001), demonstrating a 74.9% increase and an APC of 4.8%. (figure 1b, table S3) When analyzing these trends according to etiology of liver disease (table S2), we found that the absolute number of patients listed with NASH-ACLF rose significantly from 133 to 574 candidates (β=36.1, p<0.001), yielding a 331.6% percentage increase and an APC of 12.9%. Patients listed with ACLF secondary to ALD also rose by 206.3% between years 2005 and 2017 from 348 to 1,066 listed patients (β=62.2, p<0.001), with an APC of 9.8%. Although the absolute number of HCV-ACLF listings rose from 2005 to 2014 (β=15.1, p=0.005), they declined significantly from 2014 to 2017 (β=-112.8, p=0.006). This amounted to an overall 45.2% decrease with an APC of -3.9%. When accounting for the rising volume of ACLF listings over time (figure S2), there remained a significant increasing trend in ALD (β=83.7, p<0.001) and NASH (β=83.7, p<0.001) as proportions of total ACLF listings. However, HCV listings consistently declined from 2005 to 2017, with the trend accelerating downward significantly beginning in 2014 (pre-2014 β=-0.018 versus post-2014 β=-0.067; p<0.001).

In 2015, ALD became the most common etiology of liver disease among patients listed with ACLF. Furthermore, the steepest rise in the number of registrations among ALD patients occurred from 2014, with an APC of 15.4%, as compared to 6.9% between 2005-2013. In 2016, NASH surpassed HCV to become the second most common etiology. The proportion of patients listed with ACLF accounted for by NASH increased 2.4 fold (11.4% to 27.8%), while the proportion of ALD-ACLF rose 1.7 fold (29.9% to 51.7%), and the proportion of candidates with HCV-ACLF decreased by 0.65 fold (58.7% to 20.5%).

Exclusion of patients diagnosed with HCC (figure 1b, table S3) demonstrated similar trends, with NASH (β=34.9, p<0.001) accounting for the greatest percentage rise from 2005 (324.4%) and APC (12.8%), followed by ALD (β=62.3, p<0.001), with an APC of 9.8% and a percentage increase of 206.1% from 2005-2017. HCV as an etiology of cirrhosis among candidates listed with ACLF declined by 46.8%, with an APC of -4.3%.

Regional trends

We further studied etiology-based trends among patients listed with ACLF according to UNOS region. Although we acknowledge that organ allocation is no longer determined based on region, the purpose of this analysis was to determine geographic differences in the United States regarding the rise of NASH and ALD. As depicted in figure 2, the prevalence of NASH as an etiology of patients listed with ACLF increased in all regions form 2005-2017, ranging from a 200.0% increase in region 1 to a 666.7% rise in region 11. The prevalence of patients listed with ACLF due to ALD also increased throughout the United States. The smallest percentage growth for ALD as the etiology of liver disease for patients listed with ACLF was 58.8% in region 9, while the largest growth in prevalence of ALD as an etiology of cirrhosis in listed patients with ACLF was 384.6% in region 4. Aside from regions 2, 4, 5, and 6, NASH-ACLF had a greater rise in prevalence than ALD-ACLF. The number of patients listed with ACLF secondary to HCV decreased in all regions. By comparison, in figure S3 we demonstrate that in all but one UNOS region, NASH represented the greatest percentage increase among all waitlist registrations, ranging from 90.6% (region 9) to 395.7% (region 1). In region 8, the largest increase in transplant listings was due to ALD (250.0% increase), followed by NASH (242.9% increase). In figure S4 we display by UNOS region, the number of

patients listed with NASH-ACLF, along with the total number of individuals listed with NASH cirrhosis, and the proportion of listed NASH patients with ACLF. Figure S5 depicts similar data for according to region for ALD. In all regions, ALD-ACLF represented a greater proportion of the total number of listed patients with ALD, than NASH-ACLF represented among patients listed with NASH cirrhosis. The smallest discrepancies were in regions 1 (23.7% vs 19.91%, p=0.049) and region 8 (24.3% vs 20.8%, p=0.029). (table S4).

Subgroup analysis of NASH patients according to gender

We further analyzed etiology-based trends among patients listed with ACLF according to gender. (figures S6 and S7, tables S5 and S6). Among males, we found that the number of transplant candidates with ACLF due to NASH rose from 61 to 273 (347.5% increase, β=26.7, p<0.001), and the APC between years 2005 to 2017 was 13.3%. By comparison, those listed with ACLF secondary to ALD also rose between years 2005 and 2017, though percentage rise was only 167.8% (β=51.5, p<0.001), with APC of 8.6%. HCV declined as an etiology of liver disease among individuals listed with ACLF by 45.2% (β=-9.9, p=0.156), with APC of -4.5%. Among females, ALD registrants increased from 74 to 332 candidates and therefore accounted for the greatest percentage increase during this time period of 348.6% (β=18.7, p<0.001) and APC of 13.3%, whereas the number of listed patients with NASH increased from 72 to 301 (318% increase, β=19.9, p<0.001 ,APC of 12.7%). Similar to our findings in male patients, candidates with ACLF due to HCV declined between 2005 and 2017 (25.6% decrease, (β=-.75, p<0.784), APC -2.4%).

Subgroup analysis of NASH patients according to age category

We additionally analyzed trends in the distribution of age category over time, among candidates with NASH cirrhosis and ACLF. (figure 3a, table S7). Patients were grouped as: age 18-49, age 50-59, age 60-64, and age ≥ 65, based on previously published data demonstrating this categorization to accurately portray waitlist mortality.[20] There was a decline over the study period in the percentage of NASH patients in the other age categories, though this was not statistically significant. From years 2005-2016, the majority of listed patients with NASH were age 50-59, though in 2017, the majority of patients were age 65 or older. Patients age 18-49 accounted for the smallest proportion of candidates. Linear regression demonstrated a significant increase in the proportion of ACLF listings among patients age ≥65 (β=0.90, p=0.011), from 24.1% to 31.5%, as well as a significant reduction in the percentage of candidates age 18-49 (β=-0.55, p=0.006). Additionally, these trends were significantly diverging over time (p<0.001). (Figure 3b)

Waitlist outcomes

Table 2 depicts our multivariable competing risks regression analysis regarding waitlist outcomes. Regarding 28-day mortality, patients with ALD (SHR=0.82, 95% CI 0.75-0.89) and NASH (SHR=0.85, 95% CI 0.76-0.96) had lower mortality relative to those with HCV cirrhosis. The findings were similar for 90-day mortality among candidates with ALD (SHR=0.84, 95% CI 0.78-0.91) or NASH (SHR=0.84, 95% CI 0.77-0.92). Additional factors associated with death at 28 and 90 days after listing include MELD-Na score, and female gender, and increasing age category, which was the

strongest risk factor. In table S8, we display baseline characteristics at waitlist registration among patients with NASH and ALD associated ACLF who either died or were transplanted within 90 days from listing. The data indicate that relative to the other groups, candidates with NASH-ACLF who died had the greatest proportion of patient age 65 or older (28.9%, p<0.001), a smaller percentage of males (43.5%, p<0.001), and greater prevalence of renal failure (73.3%, p<0.001).

In tables 3 and 4, we display our Cox proportional hazards regression to assess the probability of mortality or LT, within 90 days after listing. Given the changing landscape in the etiology of liver disease since 2014 as demonstrated in prior studies[3, 4] and corroborated by our data, we aimed to determine whether short-term waitlist outcomes have also changed since 2014 among patients with NASH, ALD, or HCV in the setting of ACLF. We chose Cox modeling for this analysis, in order to define factors associated specifically with either transplantation or non-transplant mortality. The risk of mortality on the waiting list since year 2014 declined for patients with ALD-ACLF (HR=0.78, 95% CI 0.70-0.88) and HCV-ACLF (HR=0.76, 95% CI 0.67-0.85). (table 3) Additionally, since 2014, the probability of LT was greater for ACLF secondary to both ALD (HR=1.08, 95% CI 1.02-1.14) and HCV (HR=1.09, 95% CI 1.02-1.16). (table 4) However, for candidates with NASH cirrhosis, mortality was not lower since 2014 (HR=0.93, 95% CI 0.81-1.08), nor was the likelihood of undergoing LT greater (HR=1.08, 95% CI 0.99-1.17).

Sensitivity analysis

Given the rise in CKD among patients listed for transplantation, particularly among patients with NASH who are at high risk for this condition[21], it is possible that certain candidates with NASH cirrhosis identified as having ACLF may have been misclassified. Therefore, we performed a sensitivity analysis to assess the robustness of our findings among NASH cirrhosis patients with ACLF at listing, by removing patients who had presumed chronic kidney disease (CKD), which we defined as a creatinine of ≥ 1.5 or requirement of hemodialysis at waitlist registration, in combination with trace or no ascites.

After removal of 1,396 patients with presumed CKD, we evaluated trends for 2,795 patients with NASH cirrhosis listed with ACLF. The characteristics of these patients are outlined in table S9. Regarding national trends of patients listed with ACLF according to etiology of cirrhosis (table S10), we still found a substantial rise in the number of waitlist registrations for NASH, including an APC of 13.6% and a 325.8% increase between 2005 and 2017. These trends persisted after excluding patients diagnosed with HCC (n=39), yielding an APC of 13.7% and 320.5% increase from 2005-2017. Additionally, we analyzed trends regarding age category after removal of patients with NASH and probable CKD and found the NASH population listed with ACLF to consist primarily of patients age 65 or older, comprising 31.7% of the cohort in 2017. (table S11) Finally, in table S12, we display our Cox proportional hazards regression for the outcome of death or LT within 90 days of listing, which indicates there has change in the likelihood of either outcome since 2014.

Discussion

Our study of the UNOS database is the first to illustrate the substantial increase in the proportion of transplant candidates with ACLF associated with NASH cirrhosis. We demonstrate this rise by showing that NASH cirrhosis yields both the largest percentage increase since 2005 among candidates with ACLF, as well as the greatest annual percentage change across the study period. Our findings were demonstrated nationally, across the majority of UNOS regions, and among male patients. Although there was a prior study investigation of the rising prevalence of ACLF secondary to NASH in the United States,[22] there were limitations due to use of the Nationwide Inpatient Sample in this study, which does not contain critical laboratory data to definitively identify certain organ failures, and instead relies on diagnostic coding which is subject to misclassification. Additionally, our findings indicate that since 2014 the 90-day waitlist mortality for patients with HCV or ALD related ACLF has declined, while the probability of LT has increased; however, for NASH-ACLF, the probability of mortality or transplantation within 90 days remains unchanged. This may be partially explained by the aging of the NASH population with ACLF, as was also demonstrated in our findings.

The escalating burden of NASH is a particularly novel finding regarding ACLF, since prior studies utilizing the EASL-CLIF definition have associated ACLF primarily with ALD.[10, 23-25] In the CANONIC study, alcoholic cirrhosis accounted for 60% of the study population with ACLF, and alcohol intake was the second most common precipitant of ACLF.[10] In the US, two studies using the Veterans Administration database, corroborated ALD to be the predominant etiology of cirrhosis among those with ACLF, with NASH comprising approximately 18% of the cohort.[23, 24] Our study also

demonstrated ALD to comprise the greatest proportion of ACLF patients, though the steepest rise in waitlist registrations occurred between 2014 and 2017. Although this finding may reflect a larger burden of ALD during years 2014-2017 time period[26], it also likely corresponds to a greater willingness by centers to list patients with acute alcoholic hepatitis (AH)[27, 28], a condition which often presents with ACLF.[29] By comparison, the increase in listing of patients with ACLF associated with NASH cirrhosis is likely more indicative of an actual escalation in the prevalence of this disease among listed patients with ACLF, rather than a greater proclivity towards listing.

Though the reason as to why individuals with NASH cirrhosis develop ACLF is uncertain, one risk factor may be related to obesity. In a prior study utilizing two large registries, obesity and particularly class III obesity was found to be an independent predictor for ACLF development, among all etiologies of cirrhosis.[30] These findings were confirmed in a follow up study[24], though notably ACLF development had the strongest association with extremes of BMI, particularly being underweight or morbidly obese. A potential explanation for this finding may be due to sarcopenia in both underweight and obese patients[31], rather than obesity itself. Additionally, as opposed to ALD, no inherent precipitant for ACLF has been established among individuals with NASH cirrhosis. Based on prior literature from multicenter[32] and registry data[33], obesity has been associated with acquisition of bacterial infections, suggesting that bacterial infection may be the primary precipitant of NASH-ACLF. Given the growth in the burden NASH-ACLF, additional investigation is needed in order to better characterize this population.

In our analysis of short-term waitlist outcomes, we did not demonstrate patients with NASH-ACLF to have greater waitlist mortality as compared to candidates with

ACLF associated ALD or HCV. Instead patients with HCV cirrhosis had the highest risk for short-term waitlist mortality across the study period. Our results concerning death on the waiting list for candidates with NASH are consistent with that of prior studies utilizing the UNOS database.[34] However, in our analysis of waitlist outcomes according to era of listing, we found that since 2014, candidates with ALD or HCV related ACLF had a lower risk for death and greater likelihood for LT within 90 days, whereas for those with NASH associated ACLF, the probability of either outcome was not different. This finding is of particular interest as it suggests that patients with NASH-ACLF may be disadvantaged in the future, relative to individuals with ACLF secondary to ALD or HCV. Candidates with HCV-ACLF have the benefit of not only highly effective treatment since 2014, but also access to a donor pool of HCV infected organs.[35] Regarding ACLF associated with ALD, we believe that the greater survival and transplant probability in this population since 2014 is related to the upsurge in listing of patients with AH, as this population carries certain advantages related to LT including a median MELD-Na score of 38 yielding higher waitlist priority and a shorter median waiting time of 7 days from listing to LT.[27] Although we did not subcategorize AH in our ALD cohort due to the risk of misclassification[36], our analysis did find candidates with ALD associated ACLF to have the greatest prevalence of liver and coagulation failure, which resulted in the highest median MELD-Na score of all three patient groups.

There are additional factors that might disadvantage patients with NASH related ACLF regarding LT, compared to other etiologies of cirrhosis. We believe one of the principal reasons is the aging of the NASH-ACLF population, which at present consists primarily of individuals who are age 65 or older, while patients ages 18-49 years

comprise the smallest percentage of this group. Furthermore, our analysis indicates this trend is likely to continue. As patients age 65 or older carry a nearly two fold higher risk of death on the waiting list according to our findings, as well as a lower probability for LT[20], candidates with ACLF associated with NASH cirrhosis may potentially have the highest risk of waitlist mortality. Furthermore, a bias currently exists against considering LT for patients with NASH[37], and as the cohort of NASH-ACLF ages, there may be an increasing tendency to decline transplant evaluation for these individuals even if competitive to receive an organ offer. It is notable that compared to those with NASH-ACLF, a greater proportion of patients with ALD-ACLF were listed relative to all candidates with ALD. As we cannot determine if this discrepancy is due to a bias against listing individuals with NASH-ACLF or because ALD presents more commonly with ACLF, further exploration may be useful to evaluate the reasons for regional differences in waitlist registration.

The UNOS registry has certain strengths for this investigation, particularly the availability of a large sample size of patients with ACLF-3, across multiple regions in the United States. However, several limitations that are inherent in retrospective studies analyzing a large public database also exist in our study, primarily related to the potential for misclassification. For instance, it is possible that certain individuals were incorrectly classified as not having ACLF though they had a decompensating event such as variceal bleeding or bacterial infection, which is not captured in the UNOS database. Similarly, misclassification may also occur regarding grade of hepatic encephalopathy, as this is reported based on the subjective assessment of the treating provider. Secondly, the study utilizes the presence of mechanical ventilation as an

indicator for respiratory failure. However, the indication for mechanical ventilation is not available, and some patients may have been ventilated for airway protection due to altered mental status, whereas other patients with lung injury that qualifies as respiratory failure may have not been intubated at the time of liver transplantation. Additionally, renal failure was the most prevalent organ system failure among candidates with NASH and there is a possibility that certain patients may have been misclassified as having ACLF in the setting of chronic kidney disease. However, our sensitivity analysis likely addresses this concern. It is important to note that our study was restricted to patients listed for LT and therefore, our data should not be interpreted as representative of the overall etiology-based trends in ACLF in the US. Finally, although the current study was restricted to the US, the increasing global burden of NASH makes the data in this study highly relevant to the transplant field as a whole.[18]

In conclusion, NASH cirrhosis represents the fastest growing etiology of liver disease among patients listed with ACLF in the US as a whole, as well as within the majority of UNOS regions. Since 2014, waitlist mortality has declined and transplant probability has increased relative to before 2014 for individuals with ACLF related to HCV or ALD, but has remained similar for candidates with NASH. Regional variations in waitlist registration of ACLF patients related to NASH and ALD were observed, which requires further investigation in order to ensure equitable access to these patients. As the NASH population continues to age, it is possible that over time NASH-ACLF will have the highest risk of waitlist mortality. These findings underscore the importance of prospective research to further characterize ACLF in patients with NASH cirrhosis regarding delineating the common precipitants in order to prevent ACLF development

and understanding how to improve waitlist survival and increase the likelihood for LT in this population.

Figure legends

Figure 1a. Number of ACLF patients listed for liver transplantation by etiology

Figure 1b. Number of ACLF patients listed for liver transplantation by etiology (without HCC)

Figure 2. Regional percentage differences in waitlist registrations for patients with ACLF, between 2005 and 2017

Figure 3a. Percentage of younger (age 18-49) and elderly (age ≥ 65) patients listed with ACLF, according to etiology of liver disease

Figure 3b. Divergence in NASH ACLF listings by age category (age 18-49 versus age≥65)

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